Breast conservation and axillary management after primary systemic therapy in patients with early-stage breast cancer: the Lucerne toolbox

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Primary systemic therapy is increasingly used in the treatment of patients with early-stage breast cancer, but few guidelines specifically address optimal locoregional therapies. Therefore, we established an international consortium to discuss clinical evidence and to provide expert advice on technical management of patients with early-stage breast cancer. The steering committee prepared six working packages to address all major clinical questions from diagnosis to surgery. During a consensus meeting that included members from European scientific oncology societies, clinical trial groups, and patient advocates, statements were discussed and voted on. A consensus was reached in 42% of statements, a majority in 38%, and no decision in 21%. Based on these findings, the panel developed clinical guidance recommendations and a toolbox to overcome many clinical and technical requirements associated with the diagnosis, response assessment, surgical planning, and surgery of patients with early-stage breast cancer. This guidance could convince clinicians and patients of the major clinical advancements purported by primary systemic therapy, the use of less extensive and more targeted surgery to improve the lives of patients with breast cancer.

Introduction

Primary (or preoperative) systemic therapy (PST) is the standard of care for patients with locally advanced and large, resectable breast cancer.[1] PST should also be considered for patients with a smaller tumour burden but with a clear chemotherapy indication at diagnosis, especially patients with triple-negative or HER2-positive breast cancer.[1,2] One aim of PST is to reduce the extent of surgery, including the possibility of mastectomy[3–5] or axillary lymph node dissection.[5–7]

Patients who respond to PST and have a pathological complete response show improved survival, particularly patients with aggressive tumour subtypes (eg, those with triple-negative or HER2-positive breast cancer).[8] Improved outcomes have also been shown after PST escalation in patients with aggressive subtypes who do not have a pathological complete response.[9,10] Ongoing trials are testing whether this approach is also beneficial in patients with luminal B-like tumours (NCT01864746) and in patients with triple-negative breast cancer who have a high residual disease burden (NCT02954874). In addition to tumour stage and biology, response to PST has become a third factor in tailoring systemic treatment and postoperative radiotherapy.[11]

Although previous trials have shown important improvements in the number of patients who have had a pathological complete response to PST, these results are often not consistent with breast-conserving surgery rates.[12–15] This finding was confirmed in a meta-analysis,[16] which showed that actual breast-conserving surgery rates were moderate, even in patients who were clinically eligible for breast conservation.[17,18] Possibly, these moderate results are related to the absence of breast-conserving surgery as a surrogate endpoint along with the primary endpoint of pathological complete response.

A large meta-analysis from the Early Breast Cancer Trialist's Collaborative Group, which included 4756 patients from ten PST trials, indicated a significant increase in local cancer recurrences after PST.[3] Although these data should be interpreted with caution (eg, patients who did not have surgery were included in the data set, the timeframe of the included trials ranged from 1983 to 2002, the options for systemic therapy and surgery are now outdated, and experience with PST was inconsistent among clinicians), these findings indicate the possibility of excessive de-escalation of local treatment for some patients who were scheduled for PST, a scenario which should be avoided.

In addition to local treatment of the breast, delivering appropriate regional treatment to the lymph nodes after PST is a clinical challenge. In women presenting with clinically node-negative (cN0) breast cancer diagnosis, strong evidence suggests that sentinel lymph node biopsy after PST is feasible and safe.[2,19–21] More controversy exists with regard to women with initially limited nodal involvement (cN1) who downstage to cN0 after PST; prospective non-randomised trials have shown that, in this setting, false-negative rates of sentinel lymph node biopsy are higher than in the primary surgery setting.[19,22–24] Several new strategies for axillary staging after PST have been proposed.[25–27]

Although PST can reduce the extent of surgery, clinical trial data suggest that there is only moderate success in breast or breast tissue conservation[16] and in de-escalating axillary treatment.[21] Thus, an interdisciplinary consensus panel was convened to specifically focus on challenging

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Panel 1: **Overview of working packages**

Working package 1 (appendix pp 3–4)
Basic requirements: multidisciplinary team meetings and patient visits with clinical specialists

Working package 2 (appendix pp 5–8)
Diagnostic assessment of patients planned for primary systemic therapy: pathology, imaging, and marking of breast and axilla at diagnosis

Working package 3 (appendix p 9)
Tumour response to primary systemic therapy: optimal timepoints and modalities of response assessments

Working packages 4 and 5 (appendix pp 10–14)
Preoperative surgical plan and preoperative and intraoperative locational techniques for breast and axillary surgery

Working package 6 (appendix p 15)
Basic quality control and benchmarks, and patient reported outcomes

cases for upfront breast or axillary conservation, or both, after patients with early-stage breast cancer responded well to PST. Panellists aimed to address relevant questions, from diagnostic procedures to surgical planning and pathology assessment, based on available evidence and the clinical expertise of panellists. We report on the panel discussion and the voting and formulated a toolbox to implement strategies in the daily clinic.

Based on current available evidence and panel expertise, this Policy Review provides a practical working toolbox for the optimum pathway for surgical treatment for patients with early-stage breast cancer after PST based on chemotherapy. The toolbox consists of a comprehensive set of recommendations for the management of PST across the multidisciplinary team, with the intention of supporting physicians in optimising the pathway towards breast conservation and ultimately improving outcomes. The scope of this toolbox applies to resectable, early-stage breast cancer and is intended for use in daily clinical practice, especially for individuals who have a tumour volume exceeding 20–30% of the total breast volume. Additionally, the consensus serves as a reference tool for clinical trials that aim to address PST for early-stage breast cancer.

Data collection

A full account of how the steering committee and panel were formed, including any premeeting procedures, and measures that were implemented to ensure independence is available in the appendix (pp 1–2). The multidisciplinary steering committee consisted of seven members across five European countries and the USA, and included speciality representatives from surgery, breast imaging, radiation oncology, medical oncology, and pathology.

Any major clinical questions and statements to be addressed by the panel were defined on the basis of a typical patient journey from diagnosis to surgery in women undergoing PST. The steering committee developed six working packages (panel 1) and chose specific clinical contexts at each stage of the patient's journey. This strategy was followed up to ensure clarity of each statement during the voting process, by providing a logical sequence of clinically relevant and applicable processes for most patients in daily practice. A systematic search of the literature was not done. Because patients with locally advanced tumours (cT4) or a high axillary burden (cN2 and cN3), or both, undergo highly individualised treatment, they were not included in this consensus.

The programme proposal was endorsed by several European societies and clinical trial groups, including the European Society of Surgical Oncology, European Society for Radiotherapy and Oncology, European Society of Breast Imaging, European Society of Breast Cancer Specialists, European School of Oncology, European Society for Medical Oncology, EUROPA DONNA–The European Breast Cancer Coalition, Austrian Breast and Colorectal Cancer Study Group, International Breast Cancer Study Group, German Breast Group, Swiss Working Group for Clinical Cancer Research, Swiss Society of Senology, and Hirslanden Network of Breast Cancer Centers. Societies and clinical trial groups delegated a minimum of two representatives with specific expertise to join the multidisciplinary panel. Three patient advocates were nominated from EUROPA DONNA–The European Breast Cancer Coalition and joined the panel. Along with members of the steering committee, the final voting panel consisted of 28 representatives from 12 European countries and the USA, and covered six specialties (surgery, radiology, radiation oncology, gynaecology, medical oncology, and pathology), with one patient advocate voting. A modified Delphi method was used, which included stages of preparation, consensus, and reporting.

Before the face-to-face meeting, an anonymous feedback procedure by the steering committee was done via email, in which background information including the working packages were twice sent to panellists between January, 2019, and the face-to-face consensus meeting. On Feb 8, 2019, in Lucerne, Switzerland, there was a face-to-face consensus meeting that included 21 panellists, of which seven were steering committee members. The seven panellists who were not present voted via email within a week after the meeting. Voting was done using a digital voting system. A consensus was reached if 75% or more of all panellists agreed on a given statement, in line with commonly reported thresholds for Delphi consensus. Between 51% and 74% of agreement was defined as a majority.

The steering committee and panellists acknowledged that guideline development is possible in areas with sufficient evidence, which was usually on major issues of

local therapy. However, the committee and panellists agreed that areas of controversy should be discussed when applying a patient-centric view of the clinical experience. Additionally, several solutions might have similar outcomes, especially those concerning technical details (eg, lesion localisation can be achieved via ultrasound or a wire). Therefore, the consensus meeting sought to provide guidance on at least two levels: at the consensus level and at the clinical toolbox level.[28]

Findings

Full results of the modified Delphi process can be found in the appendix (pp 3–15). Panellists voted on 130 statements or questions. 46 (42%) statements reached consensus, a majority decision was reached in 46 (38%) statements, and no decision was reached in 23 (21%) statements. An overview describing each working package is provided (panel 1); all major statements derived from the working packages are summarised (panel 2).

Working package 1

Working package 1 outlines the basic requirements to optimise the success of preoperative therapies (appendix pp 3–4). There was consensus (93%) that patients who are undergoing PST must be presented to a multidisciplinary team meeting, and that attendance of all five core specialities (surgery, medical oncology, radiology, pathology, and radiation oncology) is required during diagnostic discussion. All panellists agreed that all staging examinations, breast imaging, and pathological work-up must be available to guide treatment decisions. A majority (61%) voted against a standard multidisciplinary team meeting discussion halfway through the chemotherapy regimen, or when there is a planned or toxicity-related change of the PST regimen. However, there was consensus (75%) for a multidisciplinary team meeting discussion for poor response or progressive disease, and a majority (68%) voted for a multidisciplinary team meeting discussion before surgery. Panellists did not reach a majority (43%) on whether a multidisciplinary team meeting is required for patients who stop PST due to toxicity or non-compliance.

There was consensus (93%) for regular clinical visits with the medical specialist responsible for the administration of PST. A majority of 64% agreed that patients undergoing PST should be seen by the specialist who will be doing the surgery (eg, general surgeon or gynaecologist); however, a majority of 57% voted against a clinical visit with a radiation oncologist before PST, because panellists considered an imaging discussion at the multidisciplinary team meeting to be sufficient and that the choice of radiotherapy will depend on the final surgical choice. There was consensus (93%) regarding the need to assess and to note the surgical options (depending on the response) in the patient chart. Panellists were almost evenly split in recommending two clinical surgeon visits (at diagnosis and at the end of PST; 46%) versus three visits (including an additional mid-term visit; 54%). No clear guidance concerning the optimal timing of surgery after PST emerged, but almost 50% of panellists stated that timing should depend on the type and intensity of the chemotherapy regimen, ranging from 2 weeks to 5 weeks after PST completion.

Interdisciplinary discussion of diagnosis and therapy at a multidisciplinary team meeting is associated with a reduction in mortality,[29] which makes this an important requirement for candidates eligible for PST. Clinicians

Panel 2: **Toolbox**

Working package 1: basis

- All patients receiving primary systemic therapy (PST) must undergo full evaluation by multidisciplinary team meetings at diagnosis
- Regular clinical visits with medical oncologist during PST
- Diagnostic and presurgical clinical visits with the surgeon allow early discussion of local therapy options

Working package 2: initial diagnosis

- Testing of oestrogen receptor, progesterone receptor, HER2, and Ki-67 expression is required in all patients receiving PST, and tumour-infiltrating lymphocyte and multigene tests should be done in selected patients
- MRI should be done in patients with specific indications, such as dense tissue, multiple lesions, unclear lesion extent, or lobular histology
- Ultrasound of the axilla is required in all patients receiving PST
- Clipping or marking of breast or axillary lesions that are classified as IVc or V according to the Breast Imaging-Reporting and Database System is preferred at diagnostic assessment
- Clipping or marking of cancer lesions before PST is mandatory

Working package 3: response assessment

- Assessment of tumour response should be done at approximately halfway through PST and at the end of PST or before surgery
- Clinical palpation can inform targeted imaging to identify progressive disease
- Aim for consistency between diagnostic imaging modality and response assessment

Working packages 4 and 5: surgery

- Offer breast-conserving surgery if the clinical response indicates stable disease or better in patients with involvement of 20–30% of breast tissue
- Breast-conserving surgery requires a clear preoperative plan for localisation, volume excision, and retrieval of breast markers
- Axillary lymph node dissection should be done in more than three clinically positive lymph nodes or matted nodes at diagnosis, or if patients have ypN1 at surgery
- Offer limited axillary surgery in patients with cN1 and clinical complete response; strict technical standards apply
- Regional nodal irradiation after limited axillary surgery and ypN0 in case of additional risk factors

Working package 6: reporting

- Document the so-called tumour scar or clip after surgical resection
- Reintervention rates of:
  - Breast due to R1: ≤30%
  - Axilla due to ypN1: ≤20%
  - Consider photographic documentation of cosmetic outcome
  - Collect patient reported outcomes

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See Online for appendix

from all five core specialties should participate in a multidisciplinary team meeting and do so with full knowledge of staging examinations and pathological work-up. The patient should be clinically evaluated regularly by the medical or clinical oncologist or gynaecologist who is administering PST, and a minimum of two clinical visits (at the start of PST and before surgery) with the surgeon will facilitate a discussion about surgical alternatives upfront. PST offers many opportunities for genetic counselling. Deleterious germline mutations could have important implications for local therapy.

Working package 2

Working package 2 indicates the recommendations for diagnostic assessment of patients planned for PST (appendix pp 5–8). There was consensus (100%) that biomarker status (eg, oestrogen receptor, progesterone receptor, and HER2) and nuclear grading should be assessed for all patients before PST. A majority (71%) was in favour of assessing Ki-67 expression with pretherapy core biopsies, and there was consensus (82%) that assessment of Ki-67 expression should be standard for all patients before PST. Among patients with hormone receptor-positive and HER2-negative breast cancer, there was consensus that gene expression assays can be useful for treatment guidance. There was consensus that assessing tumour-infiltrating lymphocyte concentrations can be useful to identify patients who have a higher likelihood of pathological complete response for triple-negative and HER2-positive breast cancer. However, panellists did not reach an agreement (25%) on whether assessing the concentration of tumour-infiltrating lymphocytes is useful or if this assessment should be done in all patients undergoing PST. When panellists were asked whether fine-needle aspiration of suspicious lymph nodes is sufficient for the diagnosis of axillary metastases, no agreement was reached.

All votes in this radiology and intervention part of working package 2 were based on a specific clinical scenario: PST given with the intent to facilitate or to allow breast-conserving surgery in women with tumour volumes exceeding 20–30% of total breast volume (the target population). Consensus (93%) was reached for the use of breast MRI in patients with invasive ductal carcinoma when there is suspected multifocality, multicentricity or unclear findings with regard to lesion extent at conventional breast imaging by mammography, digital breast tomosynthesis, and ultrasound. There was consensus (93%) that image-guided biopsy should be done for all additional lesions detected by MRI that could potentially alter the surgical plan. A majority (68%) agreed that MRI should be systematically used in patients with lobular histology. Additional guidance statements pertaining to MRI and PET imaging are detailed in the appendix (pp 5–8).

Consensus (75%) was reached for statements related to tumour marking: for all lesions that are classified as IVc and V according to the American College of Radiology Breast Imaging-Reporting and Data System Atlas (5th Edition), tumour marking should be done at the time of the first image-guided biopsy, and a marker that allows for intraoperative localisation should be used. Additional guidance statements are shown (appendix pp 5–8).

Consensus was reached for the following statements relating to axilla staging. First, clinical examination is not sufficient for adequate staging of the axilla (79% consensus) even if combined with other imaging modalities, such as mammography, digital breast tomosynthesis, or MRI. Second, any node with cortical thickening of more than 3 mm, a decrease in or absence of fatty hilum, or changes in the shape or vascular pattern is suspicious for the presence of axillary metastasis (79% consensus). Third, in case of suspected nodal metastasis, targeted axillary imaging with ultrasound is required (86% consensus). Finally, if axillary lymph node metastasis is subsequently suspected, targeted image-guided biopsy with fine-needle aspiration or core biopsy should be done (89% consensus), with one representative node being sufficient. Additional guidance statements on axillary imaging pertaining to PET–CT or PET–MRI are described in the appendix (pp 5–8).

A second set of statements addressed patients with cN1 or biopsy-confirmed metastases. Because these patients might downstage to cN0, a majority of panellists (68%) favoured a targeted approach at surgery and reported lymph node marking to be essential. The type of axillary marker that should be recommended varied greatly among panellists and no clear recommendation could be made.

To accurately predict the chances of tumour response, candidates for PST require specific interventions in their diagnostic assessment. In this setting, pathological assessment of biomarker status, nuclear grading, and Ki-67 expression is essential.[30] Although the concordance rates of Ki-67 expression can be improved by standardisation and digital image analysis,[31,32] and the results might not be equally informative in all tumour subtypes, there was consensus (82%) to routinely assess the expression of this protein. Among patients with oestrogen receptor-positive, HER2-negative breast cancer, gene expression assays are useful for treatment guidance, given that patients with oestrogen receptor-positive and HER2-negative breast cancer at a low molecular risk rarely show complete clinical remission.[33–35]

Considering breast and axillary imaging in the target population, the panel specifically recommends breast MRI in cases with suspected multifocality, multicentricity, or unclear findings with regard to lesion extent. A majority (61%) acknowledged that breast MRI is not required for women with low breast density (American College of Radiology A or American College

of Radiology B) and unifocal lesions in conventional imaging.[36,37] Axillary imaging should be based on an ultrasound,[36] although other modalities can help with estimating the actual axillary tumour burden.

Tumour marking of the breast should be incorporated into the diagnostic work-up to limit multiple interventions and to allow easy intraoperative localisation, even after 6 months of chemotherapy. The type of tumour marker that should be used varied among panellists and no clear recommendation could be made for a specific type of marker. In patients for whom lymph node metastasis is clinically suspected, a majority (61%) voted that marking a representative lymph node is important to enable targeted approaches to axillary surgery. Considering the technical detail of these approaches, almost a third (32%) of panellists abstained from the vote.

The panel did not specifically deliberate on systemic staging for distant metastasis at diagnosis. Although internationally recognised guidelines[1] agree that most patients should receive staging before PST, there is a large variation in the specific imaging modalities used in clinical practice for this purpose.

Working package 3

Working package 3 indicates the recommendations for assessing tumour response to PST (appendix p 9). A majority (54%) favoured an early (within 2 months or two cycles of PST) response assessment to identify progressive disease. Consensus (79%) was reached for assessing tumour response around halfway through PST. In cases of palpable tumours, a majority (64%) agreed that clinical palpation is not sufficient to identify response or non-response, and therefore imaging should be used for surgical planning and assessing tumour response. However, if there is clinical suspicion of progressive disease, a majority (57%) voted that clinical palpation is adequate to inform targeted imaging.

There was consensus (96%) that the imaging modality for assessing tumour response depends largely on the initial diagnostic imaging. If breast and axilla staging was successful with mammography, digital breast tomosynthesis, or ultrasound, then these modalities should also be used for the assessment of tumour response. A majority (54%) voted that assessing tumour response does not always require an objective imaging method to confirm downsizing or progression.

Multimodality radiological assessment before and during PST is mandatory to assess tumour response and is a prerequisite for surgical planning. The accuracy in predicting tumour shrinkage depends on the imaging modality, tumour biology, and availability of images taken at diagnosis, which would allow comparison.[38–40] New functional imaging techniques could have the potential to increase diagnostic accuracy, but these techniques have not been incorporated into clinical practice.[38]

As described in working package 2, MRI is used in a large number of indications within the target population, both for diagnosis and in the assessment of tumour response. In panel discussions, it became clear that clinicians valued consistency of imaging modalities throughout PST because evidence indicates that longitudinal measurements and assessment of delta change could increase accuracy.[40]

Working package 4

Working package 4 contained questions relating to the preoperative surgical plan and localisation techniques (appendix pp 10–12). Consensus (82%) was reached that breast-conserving surgery should be attempted in patients with partial response to treatment. 96% of panellists agreed that breast-conserving surgery should be attempted after complete radiological response unless there is extensive multicentricity, in which case a majority (57%) recommended no attempt at breast-conserving surgery. A majority (64%) was against breast-conserving surgery in patients with clear signs of progressive disease, but the same majority was in favour of breast-conserving surgery in the case of stable disease. No consensus was reported regarding breast-conserving surgery for patients with extensive multicentric microcalcifications. A majority (71%) was reached that breast-conserving surgery should be attempted, even in patients with contraindications for radiotherapy.

There was consensus (89%) that in a patient with a clinical complete response, the surgical specimen must contain the tumour marker. No consensus was reached on the usefulness of models that predict the risk of recurrence after PST[41,42] for the decision-making process of breast-conserving surgery versus mastectomy.

Panellists reached consensus (82%) about the importance of a clear preoperative plan, including strategies to localise lesions (either preoperatively or intraoperatively), defining the breast volume to be excised, and the importance of removing tumour markers, including the documentation of retrieval (eg, specimen radiography). Consensus (82%) was reached that a combination of complementary techniques is necessary to localise residual lesions and the marked tumour bed. For patients with complete imaging response, stereotactic localisation of a tumour marker should generally be done preoperatively. However, in some cases, ultrasound can detect clips with filler and magnetic seeds that can reliably be removed,[25,43] thus enabling intraoperative rather than preoperative invasive interventions. There was consensus (86%) for clipping the resection cavity to improve radiotherapy targeting.

In terms of techniques that could be useful to target volume excision and possibly prevent second surgeries for involved margins, panellists considered intraoperative specimen radiography (75% consensus), oncoplastic surgery techniques (71% majority), and intraoperative ultrasound (54% majority; including ultrasound visible clips) to be useful. However, these results might be

biased by abstentions from panellists whose specialties were less familiar with these techniques.

Panellists reached consensus (79%) that the so-called no ink on tumour guideline is an adequate resection margin to forego second surgery of a unifocal residual tumour after PST. In the context of a multifocal residual tumour, a majority (61%) voted that no ink on tumour also defines an adequate margin, whereas margins of 2 mm (29%) or 5 mm (4%) did not find support. For multifocal residual disease, panellists reached consensus (79%) that a multidisciplinary team meeting discussion is needed to discuss surgical margins in the context of pathology and planned adjuvant therapies.[5,44]

A small majority (54%) considered intraoperative assessment (with frozen section or imprint cytology) of the sentinel lymph nodes (in cases of macroscopic suspicion of involvement) as an option to forego second surgeries. A majority (71%) agreed that oestrogen receptor, progesterone receptor, and HER2 assessments should be repeated on the residual tumour only in cases of initially negative results.

In women with a tumour volume exceeding 20–30% of the total breast volume, PST is given with the aim of shrinking the tumour and facilitating breast-conserving surgery.[2,5,11] Studies have shown that, among patients who were initially ineligible for breast-conserving surgery but were eligible after PST, the success rate of surgery (defined as a surgical specimen with no tumour on ink) can range between 75% and 80%.[17,45] However, there are concerns about locoregional recurrence rates.[3] The panel deliberated on their recommendations concerning breast-conserving surgery. In the context of a tumour volume of 20–30% of the breast, the panel agreed that breast-conserving surgery should be attempted for all women who have a partial or complete response, but that breast-conserving surgery could also be offered to women with stable disease if technically feasible. These recommendations were based on studies that addressed the risk of local recurrence after breast-conserving surgery.[41,46] A large, retrospective meta-analysis of patients undergoing PST[47] investigated survival outcomes including local recurrence according to tumour focality and stratified by type of surgery and response. Results showed that even in patients with clinically multifocal or multicentric tumours, no increase in local recurrence was noted if margins were free of the tumour or if an excellent response (pathological complete response) was reported. Finally, the panel recommendations concerning breast-conserving surgery were always subject to shared decision making.

Detailed preoperative planning to localise lesions and determine the volume of breast tissue that should be removed should be done, particularly for patients who have a complete clinical response. A number of localisation techniques are available to identify the tumour bed, and the panel reached consensus (82%) in suggesting a combination of complementary techniques rather than suggesting a single technique.

Although the amount of evidence regarding the required tumour-free margin after PST is not sufficient,[44] no ink on tumour was considered adequate to avoid re-excision, even in the case of multifocal residual disease. We refer to a detailed report concerning the pathological assessment of breast cancer specimens after PST.[48]

Working package 5

Working package 5 concerns axillary surgery and preoperative and intraoperative localisation techniques (appendix pp 13–14). Most panellists voted that more than three disease-positive (75% consensus) or matted (68% majority) lymph nodes at diagnosis is a clear indication for axillary lymph node dissection. There was no majority (50%) on whether level III metastasis at diagnosis should mandate axillary lymph node dissection. There was consensus (86%) that not all types of lymph node involvement shown at diagnosis should indicate axillary lymph node dissection after PST.

A majority (57%) was reached for axillary lymph node dissection in cases of macrometastases at surgery but not for micrometastases (25%) or isolated tumour cells (4%). No majority was reached (46%) regarding axillary lymph node dissection in the case of unsuccessful sentinel lymph node biopsy at surgery or in the case of a contraindication for radiotherapy.

A set of statements addressed patients with cN1 who had clinical remission after PST: a majority (71%) did not consider axillary lymph node dissection mandatory. A consensus (82%) was reached that the patients with cN1 who had clinical remission can undergo alternatives to axillary lymph node dissection. When asked specifically about requirements and techniques to decrease false-negative rates, a majority (68%) agreed that three or more sentinel lymph nodes provide sufficiently low false-negative rates. Alternatively, one or more sentinel lymph nodes is sufficient if the sentinel lymph nodes include the retrieval of the clipped (at diagnosis) metastatic node (68%). A majority voted for localising the marker in the axilla at the preoperative visit (64%) and for doing the axillary lymph node dissection if the clipped node is not identified during surgery (57%).

In the context of limited axillary tumour burden (cN1) at diagnosis and clinical tumour response, panellists reached consensus (93%) that not all patients need regional nodal irradiation. A majority agreed that the indication of radiation volumes (64%) and the extent of volumes to the axilla (68%) depend on the presence of other risk factors as well. Ongoing clinical trials (NCT01872975, NCT01901094, and NCT03513614) will assess the extent of radiotherapy needed for patients with early-stage breast cancer).[6,8,19,22–25,27,49–61,62]

Panellists were asked to vote on three distinct clinical scenarios: first, varying burden of initial axillary involvement; second, varying burden of residual axillary disease after PST; and finally, patients with complete axillary response. Avoiding full axillary dissection has been

shown to be associated with a reduced risk of lymphoedema.[63] More targeted surgical approaches are especially effective in the context of PST, in which, in addition to surgery, all patients receive chemotherapy and many irradiation.[63]

For the first two scenarios, two ongoing trials—the ALLIANCE A011202 (NCT01901094) and the TAXIS trial (NCT03513614)—will provide additional insight into whether axillary lymph node dissection decreases breast cancer recurrence compared with those indicated for limited axillary surgery and regional nodal irradiation. Notably, the TAXIS trial includes patients with cN2a disease, and randomisation will be done after successfully removing marked nodes, sentinel lymph nodes, and palpable axillary disease by so-called tailored axillary surgery. For the current clinical routine, panellists indicated that axillary lymph node dissection is the standard procedure for most of the patients with cN2a disease.

Panellists deliberated in detail with regard to patients with limited axillary involvement (cN1) and clinical remission after PST. Accurate surgical staging is essential to identify patients who have nodal pathological complete response and can therefore be safely spared axillary lymph node dissection. Prospective trials have shown that the false-negative rates of sentinel lymph node biopsy exceed 10% in patients who present with axillary metastasis and convert to cN0 after PST.[19,22–24] Consequently, several techniques to lower false-negative rates have been developed, including the use of dual tracers,[6,22–24,54,55] targeted axillary dissection (eg, NCT01872975),[27,56] and marking the axillary lymph node with a radioactive iodine seed (the MARI procedure).[25,59] Panellists reached consensus (82%) that despite negative prospective trial data, selected patients can forego axillary lymph node dissection. However, high technical standards apply to these procedures.

It is important to emphasise that the panel's statements regarding regional nodal irradiation were within the context of patients with nodal pathological complete response after the initial cN1 stage. In this context, both the indication and extent of regional nodal irradiation should depend on interdisciplinary discussion with consideration to other risk factors, similar to the consensus statement issued by the St Gallen panel.[11] The St Gallen panel suggested that radiotherapy can be tailored according to the response to PST. The extent of pathologically defined remission after PST can be used to modify radiotherapy indications in combination with clinical tumour stage at diagnosis. Particularly, pathological complete response after PST can indicate that radiotherapy is not needed. One example to show this is in patients with cT3 (who have tumours larger than 5 cm at diagnosis) without other risk factors (such as multifocality), who have a pathological complete response after PST and have undergone mastectomy. The indication to carry out postmastectomy radiotherapy in these patients can be questioned.

Many patients with breast cancer and involved axillary lymph nodes can be treated with irradiation of the lymph node regions instead of with axillary lymph node dissection. Although there is only scarce evidence to replace axillary lymph node dissection with radiotherapy of only the base of the axilla (ie, the volume that would otherwise be surgically removed) without treating the more remote lymph node areas, this form of de-escalation is progressively being supported.[64]

Working package 6

Working package 6 provides details on quality assurance and indicators (appendix p 15). There was consensus (96%) that surgery should follow a clear plan with regard to preoperative localisation and that, in patients without residual tumour in the breast, a so-called tumour scar or the tumour marker should be documented by the pathologist (93%). Consensus (79%) was also reached for patients who show complete clinical response of the axilla and undergo limited nodal surgery; because lymph nodes can undergo remission without scars, either clip or scar should be documented in order to ascertain pathological complete response.

There was consensus that the rate of second surgeries due to final margin assessment should not exceed 30% (79% consensus) and the rate due to axillary involvement should not exceed 20% (86% consensus). Panellists also reached consensus (79%) that consideration of available resources, photographic assessment before surgery, before radiotherapy, and a year after the end of locoregional treatment, should be routinely undertaken to allow for evaluation of aesthetic outcome. Additionally, patient reported outcomes should be collected via standardised questionnaires to allow for the measurement of patient satisfaction and quality of life (79% consensus).[65–69]

Panellists first deliberated on basic quality control that is easy to implement and largely discussed in the context of the target population. Other than formulating a clear surgical plan, which includes localisation, panellists endorsed the need to verify correct targeting of the surgical excision for both the breast and axilla, either based on tumour markers or the documentation of a tumour scar as part of the patient report. Additionally, panellists voted on statements that can serve to guide the certification of breast centres.[70] Panellists were explicitly asked to deliberate on these statements without regarding economic or organisational issues.

Panellists strongly endorsed that second surgeries of the breast due to involved resection margins (after full pathological evaluation) should occur in a maximum of one out of three patients. This statement does not reflect strong scientific evidence but was a compromise between ensuring optimal surgical planning and allowing teams to carry out second surgeries without having to break certification criteria. Second surgeries of the axilla can occur due to clinical misinterpretation of nodal remission. In the clinical experience of the panel, pathological

evaluation of harvested lymph nodes will show residual lymph node involvement in one out of every five patients despite full clinical remission. This benchmark was also endorsed in the absence of strong scientific evidence but was well within the clinical experience of the panellists.

The assessment of cosmetic results is mainly subjective with low reproducibility.[65] In previous years, software has been developed that uses frontal photographs to objectively evaluate cosmetic results after breast-conserving surgery and increase reproducibility, such as Breast Cancer Conservative Treatment. cosmetic results (also known as BBCT.core) and Breast Analyzing Tool (also known as BAT).[65–69]

Regarding objective evaluation of health-related quality of life and patient satisfaction, the use of standardised questionnaires is recommended. There are several international standardised tools for the assessment of patient-related outcomes. The Breast Q and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 with the BR23 module (now extended to the BR45 module) are the most commonly applied tools and have been validated in various breast surgery procedures.

Discussion

This Policy Review provides a framework informed by the typical patient journey from diagnosis to local therapy in women undergoing PST. After a multidisciplinary team meeting discussion, several diagnostic assessments and interventions should be scheduled if systemic therapy precedes surgery and irradiation (panel 1). Multiple areas of controversy are discussed in specific clinical contexts, such as women with primary tumour volumes exceeding 20–30% of the total breast volume (the target population).

The toolbox (panel 2) provides recommendations for standard approaches for local therapy in the context of PST, based on the integration of data from clinical trials. However, most of our recommendations were drawn from studies with low levels of evidence, such as those doing retrospective subset analyses and those evaluating outcomes from biologically determined subtypes of breast cancer. In many instances, recommendations were also drawn from the experience of contemporary practice by the panel experts—eg, innovations in surgical technique, radiotherapy, radiology, and pathology. Endorsing and implementing this toolbox in ongoing, and planned PST trials and prospectively including surgical endpoints can strengthen the level of evidence of current recommendations and offer future patients access to more evidence-based treatments.

As in a previous publication that discussed surgical de-escalation,[28] we refrained from legally relevant terms, such as standard of care, but instead focused on providing guidance that could lead to more targeted types of surgery. Reoperation, mastectomy, and axillary dissection do not reflect poor care because all of these interventions are associated with low rates of recurrence; however, this toolbox outlines the extra efforts that are needed along the continuum of care so as to provide all local therapy options.

Finally, the clinical applications of the described recommendations have not been shown through randomised trial settings to offset the increase in local recurrence rates as previously described in the meta-analysis of the Early Breast Cancer Trialist's Collaborative Group.[3] At the same time, the panel would like to emphasise that the meta-analysis of the Early Breast Cancer Trialist's Collaborative Group[3] reflects historical data, whereas more recent cohorts from large, prospective PST trials do not show that breast conservation is associated with high local recurrence, especially in patients with favourable response and despite clinical multicentricity at diagnosis.[47] Additionally, axillary surgery de-escalation is associated with much lower rates of lymphoedema,[71] whereas an increased rate of nodal recurrence has not been documented.

Management of patients treated by PST requires a coordinated multidisciplinary approach; therefore, it was important that this guideline covered a wide range of working packages and included the expertise from a wide range of specialists. Key strengths of this programme include the methods used to identify and coordinate experts across six specialities and a wide geographical spread to represent 12 health-care systems across Europe and the USA. The inclusion of three patient advocates ensured that the patient perspective was well reflected. The programme received independent funding from the Hirslanden Klinik St Anna, Lucerne, Switzerland, and endorsement from six European societies who donated their time to the programme.

Another strength is that the panel discussed several clinical recommendations in view of costs and resources that are potentially limited. Considering this view, the panel valued having consistency in the use of imaging modalities over recommending MRI in all patients. Additionally, the panel valued incorporating the marking of tumour foci into the primary diagnostic process over incorporating costly secondary procedures; multiple tools can be used to mark and later identify the tumour bed without having to apply cost-intensive tools and technologies. In summary, in an environment where PST is given as a standard treatment and interdisciplinary communication is respected, the recommendations should be applicable without a substantial excess of costs.

Limitations of the programme reflect potential unintentional biases in guidance statements caused by abstention from voting by specialties that were less familiar with intraoperative or surgical techniques. These limitations were indicated in some of the technical consensus statements concerning techniques for marking and localising breast lesions and lymph nodes. A further source of bias might stem from the selection of the expert group, with many of the panellists having

previously investigated de-escalation strategies. A further discussion on facilitators and barriers to implementations of this guidance, as well as auditing, monitoring, and future directions, can be found in the appendix (pp 1–2).

Conclusion

Using a structured and systematic method and relying on a diverse panel of experts, we developed a practical toolbox containing detailed clinical guidance for health-care professionals. This toolbox is intended to help overcome many of the clinical and technical obstacles, including those at diagnosis, response assessment, surgical planning, and surgery. Ultimately, this guidance could convince clinicians and patients of a major clinical advance purported by PST by supporting the use of less extensive and more targeted surgery to improve the lives of patients with breast cancer.

Contributors

PD, KP, FC, CD, ITR, MJC, and PP developed the concept and design. All authors contributed to data acquisition. PD, KP, FC, GM, MR, CD, ITR, MJC, and PP did the data analysis and interpreted the data. All authors were involved in drafting the Policy Review. PD, KP, FC, GM, MR, CD, ITR, MJC, and PP critically revised the Policy Review. PD, GM, and MR did the statistical analysis. PD acquired the funding. PD, KP, FC, CD, ITR, MJC, and PP contributed to administration of the consensus meeting and received financial or material support for travel. PD, KP, FC, CD, ITR, MJC, and PP provided supervision. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

PD reports a consultancy role for Roche, Merck, AstraZeneca, Amgen, Pfizer, and research and travel grants via ABCSG, Medical University of Vienna, and Hirslanden Klinik St Anna from Cepheid (Danaher), Agendia, and Myriad. FC reports a consultant role for Amgen, Astellas, Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seattle Genetics, and Teva. ITR reports personal fees from Sirius Medical. EdA reports honoraria from Roche/Genentech, Novartis, Zodiac, and Seattle Genetics, research grants from Roche/Genentech, AstraZeneca, GlaxoSmithKline, Novartis, and Servier, and travel grants from Roche/Genentech, GlaxoSmithKline, and Novartis. ITR also reports travel grants from Roche/Genentech and GlaxoSmithKline, Novartis, research grants to her institution from Roche/Genentech, AstraZeneca, GlaxoSmithKline, Novartis, and Servier, and personal fees from Zodiac. GC reports a consultancy role with Roche, Novartis, Pfizer, Eli Lilly, Daichii Sankyo, Ellipsis, and AstraZeneca, outside of the submitted work. CD reports stock and other ownership interests with Sividon Diagnostics (now Myriad), honoraria from Novartis and Roche, a consultancy role with MSD Oncology and Daiichi Sankyo, and research funding from Myriad Genetics. CD also has patents EP18209672 and EP20150702464 pending, and a patent Software (VMscope digital pathology) pending. MG reports personal fees and travel support from Amgen, AstraZeneca, Celgene, Eli Lilly, Invectys, Pfizer, Novartis, Puma, Nanostring, Roche, Medison, and LifeBrain, all outside of the submitted work. MG has an immediate family member who is employed by Sandoz. SK is the CEO of Europa Donna–The European Breast Cancer Coalition. HMK reports personal fees from Genomic Health, outside of the submitted work. SL reports grants and honoraria from Celgene, and grants and honoraria from Roche, during the study. SL also reports grants and honoraria from AbbVie, grants and honoraria from Amgen, grants and honoraria from AstraZeneca, grants and honoraria from Novartis, grants and honoraria from Pfizer, honoraria from Seattle Genetics, honoraria from PrIME (Medscape), personal fees from Chugai, grants from Teva, grants from Vifor, grants and honoraria from Daiichi-Sankyo, honoraria from Eli Lilly, honoraria from Samsung, honoraria from Eirgenix, honoraria from BMS, honoraria from Puma, honoraria from MSD, and grants from Immunomedics, outside of the submitted work. Additionally, SL has a patent (EP14153692·0) pending. FP-L reports grants and personal fees from myriad, grants and personal fees from Nanostring, personal fees from Genomic Health, personal fees from Novartis, grants and personal fees from AstraZeneca, personal fees from Pfizer, grants and personal fees from Roche, outside of the submitted work. KP reports payment for service on speakers bureaus from the European Society of Breast Imaging, Siemens Healthineers, and IDKD 2019, and membership on the advisory board of Merantix Healthcare. WPW reports research support (a grant) from Takeda Pharmaceuticals International via Swiss Group for Clinical Cancer Research, honoraria and consultancy from Genomic Health, USA, and support paid to the Basel University Hospital for conferences and meetings from Sandoz, Genomic Health, Medtronic, Novartis Oncology, Pfizer, and Eli Lilly. PP is a medical adviser of Sordina IORT Technologies spa, starting from April 1, 2020. All other authors declare that they have no other competing interests.

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